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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/646,798	08/25/2003	Anurag Rathore	161765.00520	3621

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EXAMINER	
GUDIBANDE, SATYANARAYAN R	
ART UNIT	PAPER NUMBER
1654	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/07/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/646,798	RATHORE ET AL.	
	Examiner	Art Unit	
	Satyanarayana R. Gudibande	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 March 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34 and 39-76* is/are pending in the application.

4a) Of the above claim(s) *69-76* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-34 and 39-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/14/04,4/21/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendments to claims and specification filed on 3/29/06 have been acknowledged, and amendments to specification have been entered.

Claims 1-34 and 39-76 are pending.

Claims 69-76 have been withdrawn from further consideration as being drawn to non-elected invention.

Claims 35-38 are canceled.

Claims 1-34 and 39-68 have been examined on the merit.

Applicant's amendments to claims necessitated new ground of rejections.

New Grounds of rejection

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-34 and 39-68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jespersen, et al., Eur. J. Biochem., 1994, 219, 365-373, in view of Andersson,et al., Int. J. Peptide Protein Res., 1996, 47, 311-321, in view of US patent 5,849,535 issued to Cunningham, and further in view of Houk, et al., J. Am Chem. Soc., 1987, 109, 6825-6836.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

In the instant application, applicants claim a process for decreasing trisulfide impurity in recombinant production of a growth hormone antagonist polypeptide in genetically modified host cells. The steps involved in reducing the trisulfide impurity during the process involved contacting the impurity with a mercapto compound, growing the host cells to produce the polypeptide, purifying the polypeptide and pegylating the polypeptide.

Jespersen, et al., teaches the characterization of a trisulfide derivative of human growth hormone produced in E. Coli. The reference uses 1,4-dithiothreitol to reduce the full-length derivative of the growth hormone for electrospray mass spectroscopy (page 367, column 1). Jespersen, et al., also discuss the aspect of trisulfide formation in the E. Coli cells due to the presence of high concentration of H_2S present during cell disruption (Page 372, column 1). The trisulfide bond could be formed by a HS^- attack on a disulfide linkage of the cysteine. The mechanism is reversible and hence the liberation of H_2S was observed with the treatment of cysteine on the growth hormone (page 372, column 2). The reference does not teach the pegylation of the protein and use of functional equivalents of other mercapto reducing agents. The reference does not teach using the method for reducing the trisulfide impurity for antagonist.

Andersen et al., discloses the isolation and characterization of a trisulfide variant of recombinant human growth hormone rhGH hydrophobic variant (rhGH-HV). The growth hormone variant rhGH-HV described here has been structurally defined as a trisulfide variant of rhGH because of the presence of trisulfide bonds (abstract). The amino acid sequence of the protein shown in Figure 1(page 313), corresponds to SEQ ID NO:1 of the instant application. This clearly establishes the presence of trisulfide bonds in SEQ ID NO: 1 of the instant application meeting a part of the limitation of claim 1.

Cunningham, et al., discloses a method for the preparation human growth hormone antagonist, B-2036 variants (example V in columns 56-61), that encompass the pegylation of the growth hormone (column 64). The described method meets the limitations of the 10-50 mM tris buffer temperature, pH (column 59), and volume of the buffer used during the process (column 58). However, the method described does not use mercapto compounds as reducing agents.

The reference of Houk, et al., discusses the structure-reactivity relations for number of thiol compounds, which are functional equivalents of the compounds recited the instant application. The list of compounds (on pages 6830 and 6831) can be used individually or in combinations of others for the purpose of reducing the disulfide bonds or trisulfide linkages.

In the present application, applicants have disclosed a process for reducing the trisulfide impurity during the isolation of the growth hormone antagonist from the recombinant method in E. Coli. The process involves the use of mercapto compounds to reduce the trisulfide linkages and pegylation of the resulting growth hormone. Jespersen, et al., identifies the trisulfide bond in the growth hormone isolated from E. Coli by recombinant techniques. They have shown the use of mercapto compounds to reduce the trisulfide impurity in the preparation. Jespersen, et al.,

have also shown how the trisulfide bonds break up in the presence of mercapto compounds such as 1,4-dithiothreitol and cysteine. Andersson, et al., discloses the variant of recombinant human growth hormone that is hydrophobic due to the presence of trisulfide bonds. The amino acid sequence of protein shown in figure 1 of Andersson, et al., reference corresponds to SEQ ID NO:1 of the instant application. Cunningham, et al., have disclosed the method of preparation of growth hormone variants including B-2036, which is an antagonist. The reference also teaches the pegylation procedure for the growth hormone. Houk, et al., teaches the structure-reactivity relationships of several thiol compounds that are functional equivalents of the compounds recited in the instant application. The human growth hormone variant with substitution mutation at G120K acts as a hormone growth hormone antagonist. Therefore, it would have been obvious to one skilled in the art to use the purification method of Jespersen that uses the presence of mercapto compounds that cleaves the trisulfide linkages, because such linkages were found in the growth hormone variants shown by Andersson, et al. Hence, the method of purification that worked for the growth hormone in Jazzperson, et al., using the 1,4-dithiothreitol as the mercapto compound should work for the human growth antagonist because as evidenced by Andersson, the growth hormone variant rhGH-HV contains the trisulfide bond. The rhGH-HV variant corresponds to the SEQ ID NO: 1 of the instant application. Therefore, there would have been reasonable expectation of success given the knowledge that presence of trisulfide bond in the rhGH variant and use of mercapto compounds to reduce the trisulfide impurity in the growth hormone produced from E. Coli that worked in the case of purification of rhGH by Jazzperson should work for the variant of growth hormone of the instant application. The human recombinant growth hormone can be pegylated using the method taught by Cunningham, et al.

Therefore, it would be prima-facie obvious to combine the teachings of Jespersen, Andersson, Cunningham and Houk to develop a method for the production of growth hormone antagonist from E. Coli with reduced presence of trisulfide impurity.

Response to Arguments

It should be noted that a new ground of rejection has been in light of reference Andersson,et al., Int. J. Peptide Protein Res., 1996, 47, 311-321. However, to the extent possible, applicant's arguments have been addressed below.

Applicants argue that Examiner relies on Jespersen to establish the use of 1,4-dithiothreitol to reduce the trisulfide of human growth hormone and states that the use of functional equivalents of mercapto reducing agents and using the method for the hGH antagonist is not taught in Jespersen. Applicants allege that Examiner cites Cunningham to over come the deficiencies of Jespersen to establish the purification of B-2036 and concedes that Cunningham reference does not use mercapto compounds. Applicants further allege that Examiner relied on Houk to provide functional equivalents of the compounds recited in the instant application. Applicants point out that office concludes that there would have been reasonable expectation of success to use a mercapto compound to decrease the levels of trisulfide in an hGH antagonist. Applicants further point out that Jespersen on the contrary states: "to our knowledge trisulfide bond formation in proteins has not previously been described". Applicants argue further concurring with the office that B-2036 is an entirely different protein and has 9 amino acid changes from compared to hGH. Applicants further quote from Jespersen's reference that the

mechanism of trisulfide formation was unknown and hence there could not have been reasonable expectation of success.

Applicant's arguments filed 3/29/06 have been fully considered but they are not persuasive. Because, it should be noted that the claim 1 is recited to a process of decreasing the amount of an impurity produced in recombinant production of a growth hormone antagonist polypeptide B-2036 **of** [SEQ ID NO: 1] and contacting said impurity which is the trisulfide isoform with a mercapto compound. Jespersen teaches the characterization of hGH where the authors for the first time reported the presence of a trisulfide bridge as a contaminant in the protein preparation. Jespersen used 1,4-dithiothreitol to reduce the trisulfide bond in hGH preparation. The fact that Jespersen discovered the presence of trisulfide bond and the problem was solved by the use of a mercapto compound such as 1,4-dithiothreitol to break up the aggregate meets the limitations of the claim 1. Further, the Andersson, et al., discloses that a rhGH-HV variant of growth hormone (SEQ ID NO: 1 of instant application), also contains the trisulfide bonds as impurity. This clearly indicates that this information was available for applicants and hence the reasonable expectation of success in using a mercapto compound to disrupt the trisulfide bond formation. The argument that B-2036 is an entirely different protein compared to hGH with 9 amino acid changes is partially true. The 9 amino acid changes between the two peptides makes them chemically distinct molecules. If two molecules suffer from the presence of similar functional and structural limitations such as the presence of trisulfide impurities, then the reagent that is used to overcome the problem with one moiety can also be used to similar problem in a related case as well. Moreover, Andersson, et al., discloses the SEQ ID NO: 1 of the instant application. In this case, the use of 1,4-dithiothreitol to break up the

trisulfide bond linkage used in the hGH of Jespersen, would be useful in the case of B-2036 of SEQ ID NO: 1 to break up a similar type of trisulfide impurity. With regards to argument that Cunningham discloses the B2036 variant of hGH but does not teach the use of mercapto compound, examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the Jespersen teaches the use of mercapto compound in the characterization of hGH and Cunningham discloses the B2036 variant and pegylation of the same. Houk teaches several mercapto compounds that are functional equivalents of 1,4-dithiothreitol that can be used in breaking the trisulfide bond. Therefore, the obviousness rejection as stated in office action dated 11/29/05 is proper and maintained.

Conclusion

No claim is allowed.

Applicant's amendments to claim 1 with the incorporation of B-2036 of [SEQ ID NO: 1] necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Satyanarayana R. Gudibande whose telephone number is 571-272-8146. The examiner can normally be reached on M-F 8-4.30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

1/30/07
ANISH GUPTA
PRIMARY EXAMINER

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Art Unit 1654